REMARKS

A. Status of the Claims

Claims 1-49 were pending in the case at the time of the Office Action with claims 1-22, 39, 40, 42 and 48 having been withdrawn from consideration. Claims 24, 39, and 40 have been amended in the Amendment set forth herein to correct certain typographical errors. Support for these claims can be found generally throughout the specification, such as in the claims as originally filed. No claims have been canceled. New claims 50-52 have been added. Support for new claims 50-52 can be found generally throughout the specification, such as in the claims as originally filed and page 54, lines 18-24 of the specification. Therefore, claims 23-38, 41, 43-47, and 49-52 are currently under consideration.

B. The Claim Objection Is Overcome

Claim 24 is objected to because the word "cell" was misspelled. Claim 24 has been amended to corrected this typographical error. Therefore, this objection is overcome.

C. The Claim Rejections Under 35 U.S.C. §103(a) Are Overcome

1. The Rejections Based on Wold in View of Walczak Are Overcome

Claims 23-38, 41, 3-47, and 49 are rejected under 35 U.S.C. §103(a) as being obvious over Wold (U.S. Patent 6,627,190) in view of Walczak (C44 in Information Disclosure Statement). Applicants respectfully traverse this rejection.

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28

USPQ2d 1955, 1956 (Fed. Cir. 1993). In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure* §2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness, and that if one element is missing, a *prima facie* case of obviousness does not exist. Furthermore, the Examiner must set forth any rejection under 35 U.S.C. §103(a) with particularity. As set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc., No.* 04-1350 (U.S., Apr. 30, 2007), the analysis supporting a rejection under 35 U.S.C. §103(a) "should be made explicit," and it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR*, slip op. at 14.

There is no *prima facie* case of obviousness because there is no suggestion or motivation in either Wold or Walczak that would lead one of ordinary skill in the art to lead to the claimed invention.

Wold discloses certain replication competent adenoviral vectors that are replication-competent in TERT-expressing cells. As admitted by the Examiner, "Wold does not specifically teach using expressing TRAIL from the adenovirus vector." Action, page 5, 3rd paragraph. However, in addition to not disclosing the use of TRAIL, Wold

does not disclose the use of ***any transgene***. Furthermore, U.S. Serial No. 09/351,778, to which Wold claims priority and incorporates by reference, clearly indicates that ***transgenes are to be expressed from replication-defective vectors and not from replication competent adenoviral vectors***, particularly those that express ADP. "It is also contemplated that ADP-expressing viral vectors can be administered to neoplastic cells ***along with*** a replication defective virus that expresses an anti-cancer gene product." U.S. Serial No. 09/351,778, page 17, lines 22-24 (emphasis added). Thus, through its parent application, Wold actually teaches ***away*** from the incorporation of ***any*** transgene into a replication-competent adenoviral vector, and particularly an ADP-expressing virus.

Walczak fails to cure the deficiency of Wold with respect to motivation to practice the claimed invention. Simply put, Walczak does not even pertain to adenoviral vectors, instead simply disclosing that purified TRAIL ***protein*** can kill cancer cells (page 162, right column, 1st and 3rd paragraphs). As to the administration of gene encoding TRAIL to hyperproliferative cells, Walczak is silent, and thus is cannot begin to counter the teachings of Wold, set forth above.

Furthermore, Applicants herein submit the declaration of William S. M. Wold, one of the inventors of the above-referenced patent application (Appendix A; hereinafter "the Declaration"). Dr. Wold notes that while Walczak provides information regarding the ability of TRAIL to induce apoptosis of certain cell lines, it provides no particular suggestion or motivation to indicate that adenoviral vectors that express TRAIL and ADP can be successfully grown in cell lines or applied as an anticancer therapy. Declaration, ¶5. Dr. Wold notes that in view of the apoptosis-inducing ability of TRAIL, it is possible that expression of TRAIL may result in apoptosis of the host cells, which would be

deleterious to virus replication if it should occur before replication is complete. *Id.*, citing Chiou and White, Virology 244:108-118, 1998 (Exhibit A of Declaration). For the same reason, expression of TRAIL may be deleterious to application of any such vector as an anticancer agent if it results in apoptosis of an infected cancer cell before virus replication is complete. Declaration, ¶5. This would defeat the purpose of the goal of the Wold patent of generating oncolytic vectors that can "replicate and spread throughout the tumor not just in the initially infected cells as in the case with replication-defective vectors." Declaration, ¶5, citing Wold, col. 2, lines 51-55.

Dr. Wold describes a publication of Tollefson *et al.* (J. Virology, 75(19):8875-8887, 2001; Exhibit B of Declaration), which reports that TRAIL-induced apoptosis can be inhibited by certain adenoviral proteins, including E1B-19K. Declaration, ¶6. He notes that there is no specific discussion in the Wold disclosure that its adenoviral vectors express E1B-19K. *Id.* Thus, it is possible that expression of TRAIL in a vector set forth in the Wold patent could have resulted in apoptosis of the infected cell. *Id.*

Further, he notes that the Wold patent does not disclose whether insertion of another gene (complementary DNA) into the E3 region of the vector either 5' or 3' to the ADP gene will result in expression of the new gene or will preclude efficient expression of ADP. Declaration, ¶7. For example, since both ADP and TRAIL are expressed from the same adenovirus major late promoter via alternatively spliced mRNAs in some of the vectors of the present invention, it was possible that splicing into the ADP, TRAIL, or both coding sequences might not occur. *Id.* Still further, the mechanism by which ADP functions to facilitate the efficient lysis (disruption) of infected cells at the culmination of the virus infection is unknown. *Id.* The Wold patent does not disclose whether

expression of TRAIL may negate, augment, or modify the function of ADP. If TRAIL negates the function of ADP, then the cell lysis-promoting activity of ADP expression by the vector would be lost. *Id.* If TRAIL augmented the function of ADP, then the infected cells may lyse before virus replication is complete. *Id.* Therefore, Dr. Wold concludes that unless and until the actual studies are conducted to prepare an adenoviral vector that includes a TRAIL coding region and an ADP coding region and evaluate its anti-cancer efficacy, one of ordinary skill in the art would not be able to predict with any degree of certainty whether such a vector can be successfully applied as an anticancer agent. *Id.*

Regarding new claims 50, 51, and 52, they depend from claims 23, 46, and 47 respectively. New claims 50-52 are not obvious over Wold in view of Walczak for the reasons discussed above, and further because neither reference teaches or suggests a vector that includes an E1B-19K coding region.

In conclusion, the person of ordinary skill would not be motivated to combine Wold with Walczak, and if one were so motivated, the most it would produce would be the use of ***two vectors***, a replication-competent one coding for TRAIL, and a replication-defective one over-expressing ADP. Neither reference contemplates or suggests the use of transgenes such as TRAIL in replication-competent adenoviral vectors.

In view of the foregoing, Applicants respectfully request that the rejection of claims 23-39, 41, 43-47 and 49 under 35 U.S.C. §103 be withdrawn.

2. The Rejections Based on Henderson In View of Griffith Are Overcome

Claims 23-38, 44-47, and 49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Henderson (U.S. Patent 6,197,293) taken with Griffith et al. (U.S. Patent 6,900,185; "Griffith"). Applicants respectfully traverse this rejection.

Henderson is said to disclose an E3-deleted adenovirus vector that expresses adenovirus genes in various configurations, under the control of prostate specific control sequences. Specifically, Henderson is directed to adenoviral vectors that contain a probasin transcriptional regulatory element to regulate gene expression or replication, and are therefore limited to the dorsolateral prostate and other androgen responsive tissues (see Henderson, column 5, lines 12-37). The vectors disclosed in Henderson are ***replication-competent***. Henderson discloses the presence of E1A and E1B coding sequences, which are required for replication competence, in a variety of embodiments. For example, Henderson discloses E1A and E1B under the control of the probasin transcriptional regulatory element (see Henderson, column 22, lines 32-61). Henderson also discloses vectors such as CN702 which contain the E1A and E1B region under the control of their native promoters (see Henderson, column 46, lines 15-16). Henderson does not disclose an adenoviral vector comprising a TRAIL coding region in combination with an ADP coding region.

Griffith, either alone or in combination with Henderson, does not provide the necessary motivation to one of skill in the art to practice the claimed invention. Griffith appears to provide a general teaching that administration of TRAIL via ***replication-defective*** viral vectors leads to tumor cell death. There is no suggestion or motivation found within Griffith for a skilled artisan to incorporate TRAIL into a ***replication-competent*** adenoviral vector. Unlike the functional E1 regions disclosed in Henderson, the Action states that "Griffith teaches deleting the E1 region of the adenovirus." Action, page 8, first paragraph. A deletion of the entire E1 region as taught by Griffith, renders the resultant adenoviral vector replication-defective. Such vectors must be propagated in

trans-complementary cell lines such as 293 cells (see column 11, lines 20-35). Moreover, Griffith clearly indicates that replication-defective vectors are contemplated, stating "[i]n particular, the expression vector is a non-replicative adenovirus vector." Griffith, column 9, lines 47-48. Additionally, Griffith, in generating such vectors actively screened against replication competent adenovirus (column 11, lines 38-40). By stating a preference for only replication defective adenoviral vectors and actively screening against replication competent adenovirus, Griffith not only provides no motivation to combine the teachings of these references, but also ***teaches away*** from such a combination.

Furthermore, as set forth in the declaration of Dr. Wold (Appendix A), Dr. Wold notes that as with the Wold patent and Walczak reference discussed above, Griffith fails to provide any particular suggestion or motivation to indicate a replication-competent adenoviral vector such as taught by Henderson that expresses TRAIL and ADP can be successfully grown in cell lines or applied as an anticancer therapy. Declaration, ¶9. As discussed above, it was known in the field that TRAIL has the ability to induce apoptosis in many cell lines, and that TRAIL has cytotoxic activity against a wide variety of transformed cell lines. Declaration, ¶9, citing abstract of Walczak. Indeed, in view of the apoptosis-inducing ability of TRAIL, Dr. Wold notes that is possible that expression of TRAIL may result in apoptosis of the host cells, which would be deleterious to virus replication if it should occur before replication is complete. *Id.*, citing Chiou and White, *supra*.

Furthermore, Dr. Wold observes that even if TRAIL was expressed in one of the vectors taught by Henderson, it is possible that the infected cell could undergo apoptosis.

Declaration, ¶9. As discussed above, Tollefson *et al.* (Exhibit B of Declaration) teaches that TRAIL-induced apoptosis can be inhibited by certain adenoviral proteins, including E1B-19K. *Id.* Dr. Wold notes that is not clear whether the Henderson vectors express E1B-19K. *Id.* Since the Henderson vectors use a prostate cancer-specific promoter to drive expression of the Ad E1A gene, and in some vectors they also use another prostate-specific promoter to drive expression of the E1B genes, it is possible that even if the vectors expressed E1B-19K, not enough E1B-19K would be expressed to inhibit TRAIL-induced apoptosis. *Id.* Therefore, he notes that infection of a tumor cell with a vector of Henderson that expressed TRAIL could have resulted in apoptosis of the infected cell, which could severely limited if not abolish the ability of the vector to replicate within infected cells. *Id.* As discussed above, until actual studies are conducted to prepare an adenoviral vector that includes a TRAIL coding region and an ADP coding region and evaluate its anti-cancer efficacy, one of ordinary skill in the art would not be able to predict with any degree of certainty whether such a vector can be successfully applied as an anticancer agent. Declaration, ¶10. The present inventors made such a vector, and conducted studies to show that such vectors have anti-cancer efficacy.

As each rejected dependent claim ultimately depends from claim 23, the combination of Henderson taken with Griffith cannot render these claims obvious. Accordingly, it is submitted that claims 23-38, 43-47 and 49 are not obvious over Henderson taken with Griffith.

Regarding new claims 50, 51, and 52, they depend from claims 23, 46, and 47 respectively. New claims 50-52 are not obvious over Wold in view of Walczak for the

reasons discussed above, and further because neither reference teaches or suggests a vector that includes an E1B-19K coding region.

Therefore, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103 be withdrawn.

3. The Rejection Based on Henderson in View of Griffith and Further in View of Bruder is Overcome

Claims 23 and 41 have been rejected under 35 U.S.C. §103 over Henderson taken with Griffith and further in view of Bruder *et al.*, *J. Virol.*, 71:7623-7628, 1997 ("Bruder"). As discussed in the previous section, the combination of Henderson and Griffith does not render obvious the presently claimed invention. Bruder fails to cure the deficiency of Henderson taken with Griffith. Bruder, like Griffith, also discloses ***replication-defective*** adenoviral vectors in which the entire E1 region is deleted and which are trans-complemented with 293 cells (see Bruder, page 7624, left column, "cells and viruses"). For the reasons discussed above regarding Henderson and Griffith, there would be no suggestion or motivation to provide for a method of treating a cancer using a replication-competent adenoviral vector that includes a TRAIL encoding region and an ADP coding region. Furthermore, as noted by Dr. Wold in his Declaration, any vector of Henderson that is engineered to express TRAIL could have resulted in apoptosis of an infected cell, which would be deleterious to adenoviral replication and application of the vector as an oncolytic vector. Declaration, ¶11. Bruder does not make the claimed invention obvious because like Griffith, it does not pertain to replication-competent vectors. Therefore, an individual with ordinary skill in my field would not have found the claimed invention obvious based on Henderson, Griffith, and Bruder.

Accordingly, the combination of Henderson taken with Griffith in view of Bruder cannot render obvious claims 23 and 41.

Regarding new claims 50, 51, and 52, they depend from claims 23, 46, and 47 respectively. New claim 50 is not obvious over Wold in view of Walczak for the reasons discussed above, and further because neither reference teaches or suggests a vector that includes an E1B-19K coding region. New claims 51 and 52 depend from claims 46 and 47, respectively. Claims 46 and 47 were not included in this rejection, and therefore considered to be nonobvious in view of the cited combination of references.

Therefore, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103 over Henderson taken with Griffith in view of Bruder be withdrawn.

D. Double Patenting Rejections

1. Provisional Rejections for Non-Statutory Obviousness-Type Double Patenting

a. Claims 1-75 of Copending Application 11/057,710

Claims 23-26, 32-38, 41, 43-47 and 49 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting. Applicants understand that this is a provisional rejection because the conflicting claims have not been patented. Applicants will address this rejection further and consider whether to file a terminal disclaimer once this rejection is no longer provisional.

b. Claims 11-15, 20-22, 24, 32-44, 60-75 and 97-108 of Copending Application 09/351,778 In View of Walczak

Claims 23-26, 32-38, 41, 43-47 and 49 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting. Applicants understand that

this is a provisional rejection because the conflicting claims have not been patented. Applicants will address this rejection further and consider whether to file a terminal disclaimer once this rejection is no longer provisional.

c. Claims 28-72 of Copending Application 11/249,873 In View of Walczak

Claims 23-26, 32-38, 41, 43-47 and 49 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting. Applicants understand that this is a provisional rejection because the conflicting claims have not been patented. Applicants will address this rejection further and consider whether to file a terminal disclaimer once this rejection is no longer provisional.

2. The Non-Provisional Rejections for Non-Statutory Obviousness-Type Double Patenting

The Action rejects claims 23-26, 32-34, 36-38, 41, 43-47 and 49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-11 of Wold, in view of Walczak. The Examiner contends that the claims in Wold differ form the instant claims by not specifically teaching the expression of Trail from an adenovirus vector. The Action further argues that Walczak teaches the tumoricidal activity of TRAIL. From this, the Action concludes that the combination is obvious.

Applicants point out that with a double-patenting rejection, only the claims of Wold are used for the rejection. *MPEP* §804. III ("One significant difference is that a double patenting rejection must rely on a comparison with the claims in an issued patent or to be issued patent, whereas an obvious rejection based on the same patent under 35 U.S.C.§ 102(e)/103(a) relies on a comparison with what is disclosed (whether or not

claimed) in the issued or to be issued patent"). Thus, the available content from Wold is even less than in the §103 rejection discussed above. So, just as with that rejection, the combination of Wold and Walczak would not lead one to created a single replication-competent adenoviral vector expressing ADP and TRAIL, but instead, would at most suggest the use of two vectors, one for each gene, with the latter being replication-defective. Thus, for the reasons given above, the present claims are not obvious in view of the claims in Wold combined with Walczak. Applicants respectfully request that this rejection be withdrawn.

E. Conclusion

Applicants believe that the present document is a full and complete response to the Response to Office Action dated March 1, 2007. Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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